REMARKS

In response to the Office Action mailed May 3, 2007, Applicants have amended claims 1-5, 8, 10, 13, and 43. Claims 7, 9, 11-12, 14, 16-20, and 27-42 have been canceled and no new claims have been added. It is urged that support for all the above amendments may be found throughout the specification as originally filed. No new matter has been added. The above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the amendments, claims 1-6, 8, 10, 13, 15, 25-26, and 43 are pending in the application. Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks.

Objections to the specification

The specification is objected to because it contains embedded hyperlinks and/or other forms of browser executable code. Applicants have amended the specification to delete the hyperlink "http:www.qbiogene.com/products/adenovirus/adeasy.shtml" from pages 46 and 54 of the as-filed specification, and thus, this objection is rendered moot.

Accordingly, Applicants kindly ask the Examiner to withdraw this objection.

Rejections under 35 U.S.C. §112, first paragraph

Claim 20 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to convey to the skilled artisan that the inventor was in possession of the claimed subject matter at the time of filing of the instant application. Specifically, the Examiner asserts that the claimed invention is drawn to a nucleic acid encoding a sphingosine kinase functional equivalent, derivative of homologue thereof, or the sphingosine kinase expression product or functional derivative, homologue, analog, equivalent, or mimetic thereof. Further, the Examiner alleges that the claim does not require that the produced protein possess any particular biological activity, conserved structure, or other distinguishing feature, and thus, is drawn to a genus of nucleic acids that is defined only by sequence identity. Further, the Examiner contends that in

the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description support for the claimed genus.

Applicants respectfully traverse this basis of rejection and submit that the as-filed specification adequately provides written description support for the claimed genus of nucleic acids encoding sphingosine kinase, and functional fragments or homologs thereof.

The Examiner alleges that the presently claimed genus of nucleic acids (i.e., nucleic acids encoding sphingosine kinase, and functional fragments or homologs thereof) is not adequately described in the as-filed specification. Applicants submit that information which is well known in the art need not be described in detail in the specification. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1993). Applicants submit that "homologs thereof" is clearly defined on p. 26, lines 23-28 of the as-filed specification as a sphingosine kinase molecule which is derived from a species other than that which is being treated by the method of the invention. Applicants submit that the *mouse*, *rat*, *monkey*, *S. cerevisiae*, *S. pombe*, *A. thaliana*, and *O. sativa* sphingosine kinase sequences were known prior to the effective filing date of the instant application, and thus, in possession of the skilled artisan (Pitson et al., *The Journal of Biological Chemistry*, Vol. 277, No. 51, pp. 49545-49553, 2002). Furthermore, the skilled artisan appreciates the extremely high degree of conservation in important regions necessary for sphingosine kinase activity between such diverse species as human to rice (see Figure 1, Pitson et al. 2002; Kohama et al., *The Journal of Biological Chemistry*, Vol. 273, No. 37, pp. 23722-23728, 1998; and Pitson et al., *Biochem J.* Sep 1;350 Pt 2:pp. 429-41,2000). Thus, not only were many of the homologues for sphingosine kinase known, but the homologues all possess an extremely high degree of sequence identity in the nucleotide binding domain (see abstract, Pitson et al., 2002). Applicants submit the skilled artisan would easily recognize functional fragments and homologues of sphingosine kinases as these properties have been documented in the art. Moreover, the skilled artisan would how to perform assays for sphingosine kinase activity as such assays were well known in the art at the time of filing the instant application, and are in fact made explicit reference to in Example 1 of the as-filed specification (p. 47, lines 16-22, referencing Xia et al., *P.N.A.S.* Vol. 95, pp. 14196-14201, 1998).

Applicants respectfully submit that the skilled artisan would recognize the genus described by "nucleic acids encoding sphingosine kinase, and functional fragments or

homologs thereof" from the combination of the as-filed specification and that which was well known in the art at the time of filing the instant specification. Moreover, the skilled artisan would recognize Applicants to be in possession of such a genus, because of that which is well known in the art.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw these bases for rejection.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-20 and 25-43 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to enable the skilled artisan to make and/or use the claimed invention. Specifically, the Examiner contends that the specification fails to provide any relevant teachings or specific guidance or working examples with regard to the production of SK in vivo, by modulating the functional level of SK in a mammal resulting in the treatment and/or prophylaxis of a condition characterized by aberrant or otherwise unwanted endothelial cell function.

Applicants respectfully traverse this basis of rejection and submit that the presently claimed invention is fully enabled by the as-filed specification.

The Examiner agrees that the as-filed specification is enabling for adenoviral mediated sphingosine kinase over-expression in HUVEC cells *in vitro* to: 1) enhance the cell survival of HUVEC cells; 2) alter cell adhesion molecule expression in HUVEC; and 3) promotes tube formation, which correlates to angiogenesis. In contrast, the Examiner alleges that there is no guidance or working examples to produce a therapeutic protein in vivo, and thus, the specification is not enabling for methods treating and/or prophylaxis of a disease because the skilled artisan would have had to engage in undue experimentation to practice the invention. Applicants submit that the presently claimed invention has been reduced to practice *in vitro*, namely the transmission of an adenoviral-based transgene in order to over-express a functional sphingosine kinase molecule, which modulates endothelial cell characteristics (see Examples 1 and 2). Applicants submit that the use of in vitro experiments to establish in vivo events is, in principle, a valid methodology. Cross v. Iizuka, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985); Nelson v. Bowler, 626 F.2d 853, 856, 206 U.S.P.Q. 881 (C.C.P.A. 1980).

Moreover, Applicants contend that the skill in the art is high and that the skilled artisan would only have to engage in routine experimentation in order to successfully accomplish the claimed invention in vivo. Complex experimentation is not undue, and further, such experimentation is routine in the art of gene therapy as the Examiner points out. Applicants submit the references Lee et al. (Lee et al., Coronary Artery Disease, Vol. 16, No. 7, pp. 451-456, 2005) and Duan et al., (Duan et al., Human Gene Therapy, 18:000-000, pp. 1-10, Nov. 2007) as post-filing evidence that adenoviral vectors containing sphingosine kinase were effectively utilized in rabbit and rat animal models, respectively. Applicants submit that the post-filing evidence for reduction to practice of the presently claimed adenoviral system clearly demonstrates that Applicants methods are adequately described to one of skill in the art in order to practice the invention in an in vivo setting. Moreover, both post-filing examples clearly demonstrate the efficacy of transgenic sphingosine kinase in promoting angiogenesis and improving the outcome of ischemic failure models.

Furthermore, the method need not require the injection of adenovirus into the mammal, but rather, may comprise *in vitro* modification of the desired cells with adenoviral sphingosine kinase and subsequent transfer of said cells into said mammal in order to exert a therapeutic effect (see p.34, lines 7-15, and claim 15).

Applicants respectfully submit that a clinical reduction to practice is not a prerequisite to enable a method for treating a mammal *in vivo*. Applicants have conclusively shown that over-expression of sphingosine kinase in an adenoviral vector modulates the characteristics of endothelial cells as claimed, and thus, provides sufficient enablement for the skilled artisan to accomplish the presently claimed methods *in vivo*. Additionally, Applicants have provided two examples of post-filing reductions to practice of the Applicants methods, and thus, amply demonstrate the enabling disclosure of the as-filed specification. Furthermore, these references, contrary to those cited by the Examiner, demonstrate that the skilled artisan would not have to engage in undue experimentation in order to practice the invention as claimed.

Accordingly, in view of the above amendments and remarks, Applicants respectfully request that the Examiner carefully reconsider and withdraw these bases for rejection.

Double patenting rejections

Claims 1-3, and 5 stand rejected for non-statutory obviousness type double patenting as allegedly being unpatentable over claims 1-6, 15-20 of U.S. Patent No. 10275,686 (as written by the Examiner, see Office Action p.9 last paragraph).

Further, claims 12, 5-7, and 15 stand rejected for non-statutory obviousness type double patenting as allegedly being unpatentable over claims 1-15, 17, and 23 of U.S. Patent No. 09/977,217.

Applicants respectfully traverse this rejection and submit that the pending claims have not issued and the Examiner has not indicated that they are allowable, and thus, the present claims may be considerably amended during prosecution. As the 10/275,686 and 09/977,217 are presently owned by the same entity of the present application, Applicant requests that this rejection be withdrawn in this application with the understanding that Applicants will file a Terminal Disclaimer, if appropriate, in the instant application. Until such time as the present claims are in condition for allowance, Applicants respectfully submit that the filing of a terminal disclaimer is premature.

Further, claims 12, 5-7, and 15 stand rejected for non-statutory obviousness type double patenting as allegedly being unpatentable over claims 1-6, 32-38 of U.S. Patent No. 09/977,217. Applicants respectfully traverse this rejection and submit that claims 1-6, and 32-38 of application 09/977,217 have been canceled (see PAIR, claims listing filed July 9, 2007), and thus, this rejection is rendered moot.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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